REMARKS

Claims 1-31 are pending. Applicant confirms the election without traverse to prosecute Invention I, claims 1-8 and withdraws claims 9-31 without prejudice. Examiner has rejected claims 1-8 under 35 U.S.C. 112 second paragraph as being indefinite because of objections to claim 1. The Examiner has further rejected the claims as unpatentable over Wagner et al. in view of Kent.

Claim 1 has been amended to more distinctly point out the claimed method. Claim 32 has been added. No new subject matter is believed to have been added.

Rejection under 35 U.S.C. 112 second paragraph

Claims 1-8 stand rejected under 35 U.S.C. § 112, ¶ 2 as being indefinite.

Applicant thanks the Examiner for his helpful suggestion to overcome indefiniteness. This suggestion has been incorporated by amendment into claim 1. The reference to immobilization has been removed for clarity and placed in new dependent claim 32.

The claimed method provides an improvement in purifying a ligand-binding molecule using a customized carrier-ligand conjugate. Claim 1 as amended more distinctly describes the improvement.

The Examiner has objected to various terms used in claims 1 and 3-7 because "the specification does not provide concise definitions...". Applicants believe that these terms are clearly described in the specification.

The terms in question are "carrier", "matrix-binding molecule", "matrix-binding protein" and domain. A matrix-binding molecule is a subset of the class of carrier. A matrix-binding protein is a subset of the matrix-binding molecules. The binding domain of the protein is that part of the protein (all of the protein in some cases) involved in binding to a matrix.

(a) Carrier - A carrier is capable of binding a matrix specifically or non-specifically (pages 2, 14, 17, 18)

> The improved methods rely on the ability to create a carrier reagent which is capable of (i) binding to a matrix either specifically or non-specifically; and (ii) forming a covalent linkage with any ligand having a nucleophilic group or a thioester as a result of a simple reaction which does not require a variety of chemical reagents or sophisticated chemistry (page 14, line 24).

> The term "carrier" refers to a molecule that is capable of binding specifically or non-specifically to a matrix. A carrier that is capable of binding specifically to a matrix may here be referred to as a matrix-binding molecule (page 17, line 22)

The applicants respectfully disagree with the assertion by the Examiner that the term "carrier" is essentially defined as a matrix-binding molecule. In fact, a matrix-binding molecule is a subset of molecules referred to as carriers. The matrix binding molecule must have specificity for a matrix whereas the carrier is defined above as

capable of binding specifically or non-specifically to a matrix. An example of a carrier in the above application that binds non-specifically to a matrix and is therefore not a matrix binding molecule is paramyosin which binds nitrocellulose and nylon matrices non-specifically.

(b) A matrix-binding molecule -

Where the carrier is specific for a matrix, it is here called a matrix-binding molecule (page 2, line 23)

A carrier that is capable of binding specifically to a matrix may here be referred to as a matrix-binding molecule (page 17, line 22)

Examples of matrix-binding molecules are provided on Page 18 of the specification.

"Matrix" is defined on page 18 of the specification.

Applicants respectfully disagree with the Examiner's assertion that a definition of a matrix-binding molecule has not been defined and refers the Examiner to the definitions on page 2 and 17 cited above.

(c) A matrix-binding protein as its name implies is a specific type of matrix-binding molecule. This term has been removed for consistency from claim 7 without altering the scope of the claim.

(d) Binding Domain: The term "binding domain" is not defined in the application but is a term of art which generally means a part

or all of the protein that contains the binding activity of the protein for a matrix (see for example US 5,643,758). Consistent with this meaning, The *Glossary of Biotechnology Terms* defines "domain" as "[a] discrete continuous part of the amino acid sequence that can be equated with a particular function" (available online at biotechterms.org). *Biotech's Life Science Dictionary* defines "domain" as "[a] discrete portion of a protein with its own function (available online at biotech.icmb.utexas.edu/search/dict-search.html).

MPEP 2111.06 requires that "the words in a claim should be given their plain meaning unless the applicant has provided a clear definition in the specification". Applicants assert that the definitions provided in the application are consistent with their plain meaning.

Applicant respectfully requests that the Examiner withdraw the objections to the claims on the basis of indefiniteness.

Claim Rejection – 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) over Wagner et al. (US 6,365418) in view of Kent et al. (US 6,307,018).

Wagner

The Wagner reference describes detection of a mixture of proteins such as antibodies to evaluate gene activity. The term "Detection" is generally understood as identifying the presence of a molecule in a mixture without separating it from the mixture

whereas the term "purification" refers to isolation of a specific molecule.

*Column 32, lines 54-55: This refers to a plurality of proteins as a complex mixture. There is no suggestion here that a component be purified from the complex mixture as claimed in claim 1.

*Col 8, lines 49: This describes an affinity tag capable of binding to a matrix (organic thin film). Affinity tags have been used in this way for many years. The carrier in claim 1 is different from an affinity tag. One difference which is defined in element (a) of claim 1 of the present invention is the presence of a reactive group that enables the carrier to become covalently linked to a ligand-binding domain of choice through a thioester-nucleophile linkage.

*Col 8, 64-66: This describes how different protein capture agents can be organized in an array of hundreds of protein capture agents for binding proteins that are indicative of disease. The reference states this application can be used as a diagnostic agent. This is a detection method for molecules whose presence is uncertain in a complex mixture. It does not describe purification of a particular molecule.

* The title: The Examiner has interpreted a portion of the title of the Wagner reference (Protein capture) as sufficient support for selectively binding the ligand-binding molecule. The title states:" Arrays of protein capture agents and Methods of Use". The term

"Arrays" teaches away from the present claimed invention. An array is generally used for detection not purification. Indeed the term "detection" is presented in the second sentence of the abstract. However, there is no suggestion in the abstract of a purification method, which is the subject of the present claims.

Col 27, lines 33-42: The Examiner asserts that eluting the ligand-binding molecule as described at this citation is a step in purification. However, this section deals with eluting phage which are viruses that express certain ligands on their surface which then bind to a matrix via protein capture agents. This does not describe elution of a ligand itself as required in element (c) of claim 1.

Column 12, line 9: This describes tens of proteins (which may have unknown identity/function col 11, line 55 and may be randomly chosen, col 11, line 46) in categories of proteins, all of each category binding to the protein capture agents in a single array. This teaches away from a method for purifying a single known protein using a customized carrier-ligand.

Column 6, line 59 defines serum as a body fluid consistent with its accepted meaning. However there is no basis for deducing that this reads on the claimed method of purification.

Column 23, line 44: This teaches a method that uses a chitin-binding domain. Chitin binding domains are well known in the art.

This citation does not suggest or teach the claimed method of purification of claim 7 either alone or in combination with other cites discussed above.

The method of claim 7 requires that the carrier is a chitin-binding domain that binds to an antigen (ligand) through a thioester-nucleophilic bond and thereby provides a method for making customized conjugates for purifying any specific antibody.

Applicants respectfully assert that the Examiner has used hindsight to select phrases scattered throughout the specification to reject the present claim, which is impermissable according to MPEP 2141. There is nothing in the reference that would motivate a person of ordinary skill in the art to select the phrases identified by the Examiner and combine these teachings with Kent who describes a chemical ligation and not intein mediated ligation.

Kent

This reference describes methods for chemically ligating oligopeptides not intein mediated ligation. Furthermore, unlike the claimed method, which uses at least one recombinant protein within the carrier-ligand conjugate (linked to an intein prior to cleavage to generate the C-terminal thioester), Kent relies on only synthetic peptides as reagents for ligation.

The Kent reference does not suggest that the synthetic oligopeptides can be used for binding specifically or non-specifically

to a matrix or that the synthetic oligopeptide be used as a ligand for purifying a ligand-binding molecule.

The Examiner has cited col 6, lines 45-53 of the reference as stating "which results in a simple practical approach to protein ligation". In fact the reference states:" native chemical ligation is simple, practical and is a general approach to the total chemical synthesis of proteins providing they contain appropriate ligation sites"

Kent does not refer to ligation between a protein and a peptide but rather the synthesis of an artificial protein by ligation of a series of oligopeptides. Applicants respectfully submit that has nothing to do with either Wagner or with present claimed invention.

In summary, the Wagner patent is directed to protein arrays for detecting gene expression. Kent is directed to chemically ligating peptides. The combination of protein arrays to detect gene expression with chemical ligation does not suggest or teach the amended claimed method, which requires an intein-mediated ligation between a carrier and a ligand in a method for purifying a ligand-binding molecule. Applicant respectfully requests that the Examiner reverse the rejection.

CONCLUSION

For the reasons set forth above, Applicants respectfully request that the rejections set forth in the Official Action of February 28, 2005 be withdrawn and submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited. Applicants petition for an extension of 3 months under 37 C.F.R. 1.136 and enclose a check for $510 covering the extension fees. We authorize that any additional fees that may be due be charged to deposit account number 14-0740.

Should the Examiner wish to discuss any of the remarks made herein, please call the undersigned at the number shown below.

Respectfully submitted,

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